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GRANT NUMBER DAMD17-94-J-4340

TITLE: Genetic Counseling Using BRCA1-Linked Markers

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REPORT DATE: September 1996

TYPE OF REPORT: Annual

PREPARED FOR: Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 1996	Annual (1 Sep 95 - 31 Aug 96)

4. TITLE AND SUBTITLE
Genetic Counseling Using BRCA1-Linked Markers

5. FUNDING NUMBERS
DAMD17-94-J-4340

6. AUTHOR(S)
Henry T. Lynch, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Creighton University School of Medicine
Omaha, Nebraska 68178

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, MD 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200*

Since the initiation of this study, we have provided 14 BRCA1 and 2 BRCA2 families with information sessions held at various geographic areas of the United States. These sessions included intensive education about the natural history, genetics, surveillance and management of the hereditary breast/ovarian cancer syndrome. The limitations and advantages of DNA testing were discussed stressing potential liabilities such as fear, anxiety, and insurance and employer discrimination. Genetic counseling was provided again prior to releasing DNA test results to 181 individuals who wanted to know their mutation status. Reasons given by them for being tested were concern about their siblings and children, and about screening and/or prophylactic surgery. Seventy-six percent who were BRCA1 mutation positive would give prophylactic oophorectomy serious consideration; 35% would consider prophylactic mastectomy. No significant increase in depression was noted. Eighty-one percent who were negative for BRCA1 were extremely happy and relieved. A small subset (4%) experienced survivor guilt. We continue to learn about genetic counseling as a result of this experience and to accumulate information relevant to its psychological components through collaboration with Caryn Lerman, Ph.D. BRCA1 and BRCA2 mutations have been identified in an additional 27 families and will be available for future study.

14. SUBJECT TERMS	15. NUMBER OF PAGES
BRCA1, Genetic Counseling, Breast Cancer, Psychological Monitoring, DNA Markers, Surveillance, Humans, Anatomical Samples	33
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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9/3/96

PI - Signature Date

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INTRODUCTION

Molecular genetic research became highly pertinent to hereditary breast cancer (HBC) when Hall et al [1] described families with early-onset familial aggregations of breast cancer that were linked to the D17S74 locus on the long arm of chromosome 17. The gene is now referred to as BRCA1. Following this report, Narod et al [2] studied five large hereditary breast/ovarian cancer (HBOC) families from the Creighton HBC resource and found three of them to be positive for linkage to this BRCA1 locus. BRCA1 is a large gene which contains twenty-two coding exons distributed over approximately 100kb of genomic DNA. It produces a protein of 1863 amino acids. Shattuck-Eidens et al [3] found that 86% of the 37 different BRCA1 mutations which have been identified were either frameshifts, nonsense mutations, or splice mutations. These presumably lead to premature truncation of the BRCA1 protein.

A second susceptibility gene, BRCA2, was mapped to chromosome 13 in 1994 [4] and was identified in 1995 [5]. The majority of families with cases of male breast cancer appear to be associated with BRCA2. BRCA2 confers a high risk of breast cancer, and a low risk of ovarian cancer (≈10-20%).

These molecular genetic advances have provided a unique opportunity to counsel hereditary breast cancer family members, and to offer members the opportunity to be gene tested once they understand the positive as well as negative aspects of knowing their gene status.

Follow-up genetic counseling is essential.

Goals and Objectives

The initial goal of our study supported by the Department of Defense was to evaluate the impact of genetic counseling in HBC and HBOC families where BRCA1 had been identified. With the identification of BRCA2, we are now also including families with this mutation from our resource. This study is designed to demonstrate the feasibility of genetic counseling for HBC and HBOC, and to evaluate the impact of counseling on psychological state and medical behavior. The study is also designed to examine predictors of adverse consequences that could evolve from genetic testing. This information may then enable physicians and genetic counselors to anticipate and prevent problems in individual patients.

BODY

Progress to date in our study of genetic counseling based on BRCA1 and BRCA2 linked markers has been extremely well-targeted and productive. The schematic for this study is shown in the Figure.

The search for germline mutations is performed in collaboration with Steven Narod, M.D., of Women's College Hospital, Toronto, Canada, and Gilbert Lenoir, Ph.D., D.V.M., in Lyon, France.

Eligible members of BRCA1 and BRCA2-linked families receive an

introductory letter, followed by a baseline, structured telephone interview administered by a trained interviewer at Georgetown University under the direction of Caryn Lerman, Ph.D., a clinical psychologist/geneticist at Georgetown University, Washington, D.C. About four weeks later, these individuals have an opportunity to attend an education session, referred to as a Family Information Service (FIS) at which time information about gene linkage, hereditary breast cancer and surveillance measures are again reinforced prior to individual counseling and disclosure of genetic test results for breast-ovarian cancer susceptibility.

All genetic counseling and testing is provided by, and/or supervised by Dr. Lynch and his colleagues. Structured telephone interviews are conducted from Georgetown University at one-, six-, and twelve-months following genetic counseling to evaluate the impact of disclosure of genetic information.

Results

Since the initiation of this study, 14 BRCA1 families and 2 BRCA2 families have been counseled and 246 family members have been advised of their individual gene status (Table 1). Preliminary results were presented at the meetings of the American Society of Clinical Oncology, Philadelphia, PA, May, 1996, and a report has been published [6]. (Appendix). A manuscript has also been submitted to Cancer describing our genetic counseling experience with the 14 BRCA1 families.

An additional 27 families (245 individuals sampled) have had a mutation identified and will be counseled. Twenty-three families (148 individuals sampled) are still being evaluated. Thirty-one families (405 individuals sampled) do not, to date, have an identifiable mutation on either the BRCA1 or BRCA2 genes.

Table 2 describes the demographic characteristics of the fourteen BRCA1 families who received education at family information sessions (FIS) and/or underwent DNA testing and genetic counseling. Initially, as part of our formal linkage analysis, informative married-in spouses of family members in the direct lineage underwent DNA testing. This accounts for the fact that the total number of family members was 3,678, of whom 2,549 were direct blood line relatives.

Table 3 describes cancer of all anatomic sites in concert with those individuals who are gene positive, inclusive of obligate gene carriers, versus those who are gene negative or wherein the gene status is unknown. As expected, the overwhelming majority of these patients had carcinoma of the breast and/or ovary occurring in the gene positive/obligate gene carrier individuals.

There was a slight excess of colorectal cancer among the gene positive/obligate gene carrier class (7 cases) versus the individuals in the gene negative category. However, the gene status was unknown for eight individuals, therefore, the interpretation of whether colorectal cancer occurs in excess in the

14 BRCA1 families remains elusive [7].

The issue of prostate cancer has similar limitations. Two individuals were gene positive/obligate gene status, while two were gene negative, and seven were gene status unknown. The same concern applies to malignant melanoma where three patients were gene positive/obligate gene carrier status, three were BRCA1 negative, and two were gene status unknown. Interestingly, a sarcoma occurred in two gene positive, but none in gene negative patients, but again the numbers are too small for interpretation. The remainder of the cancer sites were not informative with respect to their BRCA1 status, but the data is presented here because of the need to publish findings pertaining to cancer of <u>all</u> anatomic sites among individuals from BRCA1 families wherein germline testing has been performed.

The reasons cited by family members <u>at baseline</u> telephone interview for wanting <u>BRCA1</u> testing and for not wanting testing were evaluated. The most widely cited reasons for wanting testing were to learn about one's children's risks and to increase use of screening tests. Of interest, almost one-half of individuals surveyed reported childbearing decisions as a "very important" reason for wanting <u>BRCA1</u> testing. This is surprising, since reproductive decision making generally is not a focus in genetic counseling for cancer susceptibility. Overall, fewer individuals reported strong reasons for not having testing. This is consistent

with the high level of acceptance of testing in this population. However, concerns about the effect of testing on one's family and worries about losing health insurance were cited most frequently as barriers to receiving BRCA1 test results.

Table 4 shows the demographic characteristics of the 181 blood line relatives from the 14 BRCA1 families who were counseled, tested, and received results of their individual DNA testing.

We examined whether persons who came forward for BRCA1 testing had different sociodemographic backgrounds than those who declined, a finding which was supported by our data. Individuals who decided to be tested were predominantly female, under age 50, had at least a high school education, and had health insurance. Thus, BRCA1 test decliners were mostly males over age 50 who had not completed high school and had no health insurance. In a logistic regression model, the following factors were significant independent predictors of acceptance of testing: gender (OR=3.8, CI=1.8-8.1), age (OR=2.9, CI=1.3-6.2), education (OR=3.4, CI=1.1-11.2), and health insurance status (OR=5.1, CI=1.5-17.0). Thus, females were almost four times more likely than males to request testing; individuals under age 50 were 3½ times more likely than those over age 50; and individuals with health insurance were about five times more likely than those who did not have insurance [6].

Table 5 provides information about emotional responses among

individuals who received their BRCA1 result. Not unexpectedly, those receiving BRCA1 positive information had more emotional responses of sadness when compared to the relief obtained among those who received BRCA1 negative information.

Short-term Impact of BRCA1 Testing on Depressive Symptoms. The psychological and behavioral impacts of BRCA1 testing are being evaluated using validated psychometric tools that are administered during baseline and follow-up telephone interviews. These interviews are conducted with individuals who test positive, negative, and with those who decline testing. Outcomes of interest in this study include perceptions of risk, depression, functional health status, screening behaviors, and medical and reproductive decision-making.

Depression symptoms reported at baseline by individuals in these HBOC families do not differ from general population norms for depression using the Center for Epidemiologic Studies Scale [8]. This is somewhat surprising in light of previous studies showing elevated distress levels in women at risk for breast cancer [9,10]. It is possible that members of hereditary breast cancer families develop stronger coping mechanisms as a result of repeated experiences of having relatives diagnosed with cancer.

Following disclosure of BRCA1 status, carriers show a slight elevation in depressive symptoms over time (about .10 standard

deviations), while noncarriers show a slight decline in depression (about .25 standard deviations). These changes in depression in carriers and noncarriers are not statistically or clinically significant.

Tables 6 and 7 depict our interpretation of the attitudes about surveillance and prophylactic surgery among BRCA1 positive versus BRCA1 negative patients. As expected, a significantly larger number of individuals in the BRCA1 positive category (32%) had already manifested carcinoma of the breast and had undergone mastectomies when compared to those who were BRCA1 negative (where only 6% had already manifested carcinoma of the breast) (p= .001). Thirty-two percent of patients in the BRCA1 positive category and 22% in the BRCA1 negative category had considered prophylactic mastectomy prior to receiving their results. In contrast, 35% in the BRCA1 positive status category contemplated prophylactic mastectomy after receiving their results, but none of the negative women continued to consider this option (p= .012).

It was of interest that 73% of BRCA1 positive individuals had considered prophylactic oophorectomy <u>prior</u> to receiving their results, and 40% of those who were negative for BRCA1 had considered prophylactic oophorectomy prior to receiving their results (p= .002). However, after receiving findings that their status was positive for BRCA1, 76% considered prophylactic oophorectomy, while none in the negative BRCA1 category considered

prophylactic oophorectomy (p= .001).

Insurance Issues

About one-fourth of the individuals in both BRCA1 positive and BRCA1 negative categories were concerned about their potential for insurance discrimination. In a sample of 88 individuals tested for BRCA1 mutations, 4 of them indicated problems in obtaining or maintaining insurance; however, in each of these cases the difficulties predated receipt of test results. Four out of 38 individuals who tested positive indicated changes in their insurance since testing; however, these changes were unrelated to genetic testing [6]. Our preliminary data indicate that insurance concerns may have an effect on decisions to receive BRCA1 testing and on medical decision-making. For example, 18% of mutation carriers indicated that insurance concerns affected their decisions about receiving prophylactic surgery. Thus, it is critical that the potential for insurance discrimination be addressed during the pre-test education session.

CONCLUSION

While these preliminary results are encouraging, caution must be taken in generalizing to all individuals who may participate in BRCA1 testing. Individuals in this study received extensive education and counseling as part of their involvement in prior linkage studies. The psychological effects of BRCA1 testing may differ for individuals who are less aware of their personal risk

and who receive test results outside of a controlled research setting. In addition, patients' scores on the depression measure at one-month follow-up show large standard deviations. This suggests that there is substantial variability within the groups of carriers and noncarriers in their responses to testing. This supports the clinical observation that individuals vary widely in how they respond psychologically to genetic information. Once sufficient numbers of individuals have been accrued to this trial, it will be important to identify and characterize the subset of participants who may experience adverse effects following receipt of positive or negative results of BRCA1 testing in all areas that are being evaluted in our study.

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Figure

Design of Prospective Study of BRCA1 and BRCA2 Testing

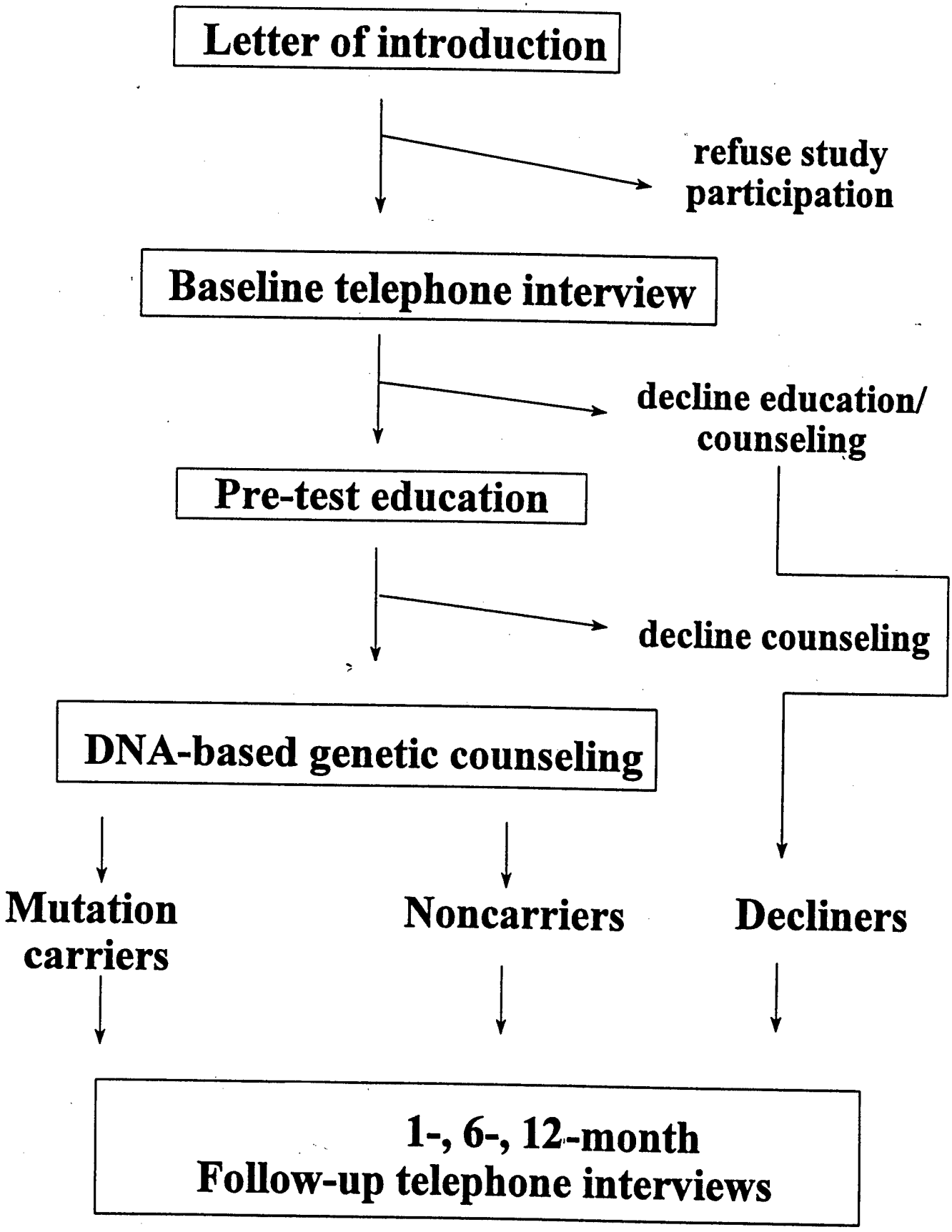

Table 1

COUNSELED INDIVIDUALS

FAMILY	DATE OF FIS
BRCA1	
2775	7-9-94
1234	8-20-94
1813	1-29-95
2090	2-18-95
2770	3-18-95
2651	4-22-95
1973	5-27-95
2944	5-27-95
3079	6-10-95
1816	8-19-95
1086	10-7-95
2749	10-28-95
1252	10-29-95
2850	3-13-96
BRCA2	
2932	1-13-96
3433	5-11-96 & 7-20-96

Table 2. Demographic characteristics of 14 BRCA1 families.

Total number of family members:	3678
Total number of blood relatives:	2549
Total number of family members educated about HBOC and the role of genetic testing:	253
Adults married into the family (not blood relatives)	41
Genetic testing status of 388 family members (of direct lineage > 18 y.o.a.) DNA sampled:	
Gene positive:	145
Gene negative:	174
Pending	58
Ambiguous	11
Total number counseled and given gene status.	181
Gene positive	78
Gene negative	100
Ambiguous	3

Table 3. Cancer sites in 238 members of 14 BRCA1 families.*

Site	Total	Gene positive/Obligate gene carriers	Gene Negative	p-value	Gene status unknown
Individuals with cancer at any site	238	114	21		103
Individuals with cancer at each specific site					
Breast	109	74	7	**	28
Ovarian	43	30	2	**	11
Colorectal	18	7	3	0.36	8
Lung	13	2	1		10
Cervical	13	1	5		7
Prostate	11	2	2	0.11	7
Cancer site unknown	9	3	0		6
Malignant Mel	8	3	3		2
Bladder	4	0	0		4
Pancreas	3	0	0		3
Kidney	2	0	0		2
Stomach	2	1	0		1
Wilm's Tumor	2	0	0		2
Leukemia	2	0	0		2
Lymphoma	2	0	0		2
Omentum	2	1	0		1
Sarcoma	2	2	0		0
Gall Bladder	2	0	0		2
Uterine	1	0	0		1

Table 3 - CONTINUED

Liver	1	0	0	1
Abd/Csu	1	1	0	0
Esophogial	1	0	0	1
Brain Tumor	1	0	0	1
Gyn Ca Unknown	1	0	0	1
Hodgkins	1	0	0	1
Thyroid	1	0	1	0
Mesentary	1	0	0	1
Malignant Schwannoma	1	0	0	1
Retroperitoneal	1	1	0	0

*20 individuals have cancer at two sites (e.g. breast/ovarian or breast/lung) and have been counted once for each primary cancer site. Therefore, totaling any of the columns will result in a figure higher than that reported in the "cancer at any site" row.

**Not computed; breast and ovarian cancer status and gene carrier status are perforce related.

Table 4. Demographic characteristics and reasons for seeking risk assessment in 181 counseled members of 14 BRCA1 families.

Sex	Number	(%)
Male	46	(25)
Female	135	(75)
BRCA1 Cancer Affected	32	(18)
Age at Time of Counseling, years		
Mean	42	
Range	19-84	
Reason for seeking risk assessment		
Children and/or family	102	(56)
Surveillance	54	(30)
Curiosity	31	(17)
For possible prophylactic surgery	13	(7)
Relieve anxiety	10	(5)
For research purposes	9	(5)

Table 5. Genetic test results, and emotional response to recieving results for 181 members of 14 BRCA1 families.

BRCA1 mutation	Number	(%)
Positive	78	(43)
Negative	101	(55)
Ambiguous	3	(2)
Emotional Response		
BRCA1 Positive		
Appeared to be Sad/crying	28	(36)
Appeared not to be surprised	21	(27)
Claimed to feel guilty	6	(8)
Appeared to be angry	5	(6)
Claimed a sense of relief	3	(4)
No apparent reaction	15	(19)
BRCA1Negative		
Appeared to be happy/relieved	81	(80)
No apparent reaction	10	(10)
Appeared to be surprised	8	(8)
Claimed feelings of survival guilt	4	(4)

Table 6. Surveillance practices and attitudes toward prophylactic mastectomy in 135 female members of 14 BRCA1 families.*

	Number (%)				
	BRCA1 Positive		BRCA1 Negative		p-value
Summary of Bilateral Mastectomies Prior to the Counseling Session					
Number of women (n)	57		78		
Mastectomy for Cancer	18	32%	2	6%	0.001
Prophylactic Mastectomy	5	9%	7	9%	ns
Mastectomy (Other medical indications: fibrocystic disease, etc)	3	5%	1	1%	ns
Breast Surveillance Prior to the Counseling Session (excluding women who have had bilateral mastectomies)					
Number of women (n)	31		68		
Mammography	24	77%	55	81%	ns
MD Exam	26	84%	59	87%	ns
Self Breast Exam	18	58%	35	51%	ns
Considering Prophylactic Mastectomy (excluding women who have had bilateral mastectomies)					
Number of women (n)	31		68		
Before recieving results	10	32%	15	22%	ns
After recieving results	11	35%	0	0%	0.012

* The data from one female with ambiguous results has been excluded

ns = not significant

p-values from Fisher's exact test (2 tailed)

Table 7. Surveillance practices and attitudes toward prophylactic oophorectomy in 135 female members of 14 BRCA1 families.*

	Number (%)				
	BRCA1 Positive		BRCA1 Negative		p-values
Summary of Bilateral Oophorectomies Prior to the Counseling Session					
Number of women (n)	57		78		
Oophorectomy for Cancer	4	7%	0	0%	ns
Prophylactic Oophorectomy	11	19%	10	13%	ns
Oophorectomy (Other medical indications: dysmenorrhea, etc.)	5	9%	10	13%	ns
Ovarian Surveillance Prior to the Counseling Session (excluding women who have had bilateral oophorectomy)					
Number of women (n)	37		58		
CA125	3	8%	6	10%	ns
Ultrasound	8	22%	12	21%	ns
Considering Prophylactic Oophorectomy (excluding women who have had bilateral oophorectomy)					
Number of women (n)	37		58		
Before recieving results	27	73%	23	40%	0.002
After recieving results	28	76%	0	0%	0.001

* The data from one female with ambiguous results has been excluded

ns = not significant

p-values from Fisher's exact test (2 tailed)

Reprinted from JAMA ® The Journal of the American Medical Association June 26, 1996 Volume 275

APPENDIX

Original Contribution

BRCA1 Testing in Families With Hereditary Breast-Ovarian Cancer

A Prospective Study of Patient Decision Making and Outcomes

Caryn Lerman, PhD; Steven Narod, MD, FRCPC; Kevin Schulman, MD; Chanita Hughes, MS; Andres Gomez-Caminero, MPH; George Bonney, PhD; Karen Gold, PhD; Bruce Trock, PhD; David Main, MS; Jane Lynch, RN; Cecil Fulmore, MS; Carrie Snyder, RN; Stephen J. Lemon, MD, MPH; Theresa Conway, RN; Patricia Tonin, PhD; Gilbert Lenoir, DVM; Henry Lynch, MD

Objectives.—To identify predictors of utilization of breast-ovarian cancer susceptibility (*BRCA1* gene) testing and to evaluate outcomes of participation in a testing program.

Design.—Prospective cohort study with baseline interview assessment of predictor variables (eg, sociodemographic factors, knowledge about hereditary cancer and genetic testing, perceptions of testing benefits, limitations, and risks). *BRCA1* test results were offered after an education and counseling session in a research setting. Outcome variables (including depression, functional health status, and prophylactic surgery plans [follow-up only]) were assessed at baseline and 1-month follow-up interviews.

Participants.—Adult male and female members (n=279) of families with *BRCA1*-linked hereditary breast-ovarian cancer (HBOC).

Results.—Of subjects who completed a baseline interview (n=192), 60% requested *BRCA1* test results (43% of all study subjects requested results). Requests for results were more frequent for persons with health insurance (odds ratio [OR], 3.74; 95% confidence interval [CI], 2.06-6.80); more first-degree relatives affected with breast cancer (OR, 1.59; 95% CI, 1.16-2.16); more knowledge about *BRCA1* testing (OR, 1.85; 95% CI, 1.36-2.50); and indicating that test benefits are important (OR, 1.45; 95% CI, 1.13-1.86). At follow-up, noncarriers of *BRCA1* mutations showed statistically significant reductions in depressive symptoms and functional impairment compared with carriers and nontested individuals. Individuals identified as mutation carriers did not exhibit increases in depression and functional impairment. Among unaffected women with no prior prophylactic surgery, 17% of carriers (2/12) intended to have mastectomies and 33% (4/12) to have oophorectomies.

Conclusions.—Only a subset of HBOC family members are likely to request *BRCA1* testing when available. Rates of test use may be higher in persons of a higher socioeconomic status and those with more relatives affected with breast cancer. For some high-risk individuals who receive test results in a research setting that includes counseling, there may be psychological benefits. More research is needed to assess the generalizability of these results and evaluate the long-term consequences of *BRCA1* testing.

(*JAMA*. 1996;275:1885-1892)

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THE ISOLATION of the *BRCA1* gene offers an unprecedented opportunity for high-risk members of families with hereditary breast-ovarian cancer (HBOC) to learn whether they carry a cancer-predisposing mutation.[1] Females found to carry a mutation in *BRCA1* have an 80% to 90% lifetime risk of breast cancer, a 40% to 65% lifetime risk of ovarian cancer, and an increased risk of colon cancer.[2,3] Male mutation carriers are at increased risk for prostate and colon cancer and can also transmit breast-ovarian cancer susceptibility to their daughters.[3] Early identification of *BRCA1* mutation carriers within HBOC families can allow for targeted surveillance and management strategies.[4-6]

For editorial comment see p 1928.

At present, little is known about whether high-risk patients from HBOC families will want to know their mutation status or how they will make decisions about undergoing *BRCA1* testing. Preliminary reports indicate that there is strong interest in *BRCA1* testing, both in the general population and in high-risk families.[7-10] However, past experiences with Huntington disease (*HD* gene) and cystic fibrosis (*CF* gene) have shown that usage rates of genetic tests may be substantially lower than anticipated based on stated intentions to receive a hypothetical genetic test.[11-14] For example, prior to the initiation of testing for the *HD* gene, two thirds of at-risk individuals expressed strong interest in testing.[15,16] Following the introduction of predictive testing programs, fewer than 15% of those who initially expressed interest participated.[11]

In deciding whether to have *BRCA1* testing, patients must weigh complex information about the potential benefits of testing against the limitations and possible risks of this new technology. These limitations and risks include uncertainties inherent in cancer risk figures,[2] the absence of proven strategies for preventing cancer in carriers (including surgical prophylaxis),[17] the risk of genetic discrimination in employment or in obtaining or maintaining insurance,[18] and the potential for negative psychological consequences of learning one's genetic status.[6,19,20] Models of consumer health behavior[21,22] can be used to understand better the ways that patients will process this complex information in deciding whether to be tested for *BRCA1* mutations. These frameworks predict that patients would acquire knowledge about the inheritance of breast-ovarian cancer susceptibility and about the test itself. This knowledge would then shape their perceptions of the benefits, limitations, and risks of being tested. Perceptions of the importance of the benefits of *BRCA1* testing would be expected to facilitate test use, while concerns about the limitations and risks should hinder use of this test.

For individuals who decide to have a *BRCA1* test, adverse psychological consequences are considered to be a potential risk.[20] This concern is based on anecdotal reports of participants in genetic linkage studies[6,19] and on the results of studies of women's anticipated emotional reactions to a hypothetical *BRCA1* test.[8,9] As yet, however, there are no published empirical accounts of the effects of *BRCA1* testing on participants' psychological and functional health status. The importance of conducting a systematic evaluation of genetic testing outcomes was underscored by a major prospective study of genetic testing for Huntington disease.[23] In contrast to the serious adverse psychological effects of genetic testing for Huntington disease that had been anticipated based on anecdotal reports,[24] the prospective study found that testing had long-term psychological benefits—both for carriers and for noncarriers of *HD* gene mutations.

To fill the gap in our knowledge of patient decision making and the outcomes of *BRCA1* testing, we conducted a prospective observational study of 279 members of *BRCA1*-linked HBOC families. This study had 3 principal goals: (1) to examine predictors of decisions to receive *BRCA1* test results, including sociodemographic factors, knowledge, and perceptions of the benefits, limitations, and risks of testing; (2) to evaluate the effects of *BRCA1* testing on psychological and functional health status; and (3) to evaluate how testing influences participants' medical decisions. At present, it is recommended that *BRCA1* testing be provided only to members of high-risk families in the context of research protocols.[25,26] By identifying factors associated with actual utilization in these studies, we can estimate the magnitude of the demand for *BRCA1* testing and identify the characteristics of those who are likely to request such testing. In addition, a better understanding of patient decision making is necessary to guide the development of educational materials and informed consent protocols for *BRCA1* testing. Finally, to the extent that we can delineate the psychosocial effects of *BRCA1* testing, we will be better able to provide counseling and to attend to participants' psychosocial and medical needs.

METHODS

Study Population

Eligible subjects included 279 women and men, aged 18 years and older, who are members of 13 extended HBOC families from a registry maintained by the Creighton University Hereditary Cancer Institute. These families were enrolled into a prospective observational study during the period from July 1994 through November 1995. These families were selected from the registry because the *BRCA1* mutations (and in 1 family, a multipoint lod score of 6.2) had previously been identified.[27] The study sample included unaffected at-risk family members (without cancer at present) as well as family members affected with cancer. Affected family members were included because, in some cases, cancers were sporadic and not due to inherited susceptibility. The 38 affected individuals included 21 women with breast cancer, 4 women with ovarian cancer, 3 women with breast and ovarian cancer, 2 men with prostate cancer, and 8 patients with other cancers. Subjects were considered ineligible for this study if they had a psychiatric or cognitive disorder which precluded informed consent (1 mentally retarded subject was excluded based on this criterion).

The families under investigation had participated in prior genetic studies.[28,29] As part of these prior studies, family members had received written educational materials about the genetics and natural history of HBOC, although none had received the results of *BRCA1* testing prior to the current research project.

Procedures

All study procedures had been approved by the Creighton University Institutional Review Board. Eligible male and female members of these extended families received an introductory letter explaining the prospective study and inviting them to participate. Individuals who did not wish to be contacted for the interview returned a self-addressed stamped postcard to the investigator (these individuals were still offered *BRCA1* testing and their decisions were recorded). Those who did not decline to be interviewed were contacted within 2 weeks to obtain oral consent for the baseline telephone interview. It was stressed that agreeing to the baseline interview did not obligate them to participate in the education session or to receive their *BRCA1* test results. A professional interviewer from Lombardi Cancer Center conducted a 40-minute structured telephone interview 1 to 2 months prior to the education session and the offer of *BRCA1* test results. Measures included sociodemographic characteristics; medical history; baseline levels of knowledge; baseline perceptions of the benefits, limitations, and risks of *BRCA1* testing; and depression and functional health status (see description of measures below).

All family members were subsequently invited to attend an education session on *BRCA1* testing. These 1- to 2-hour sessions were conducted on a family-by-family basis through a series of trips to a geographic area central to most family members. Individuals who were unable to attend the education session for their family were given the option of traveling to Creighton University (funds were available through the research grant to support this travel) or to receive the education by telephone. An oncologist/geneticist (H.T.L.) conducted all education sessions following a semistructured protocol. After written informed consent was obtained, the following topics were addressed: (*a*) inheritance of breast-ovarian cancer susceptibility; (*b*) cancer risks associated with *BRCA1* mutations, including breast, ovarian, colon, and prostate cancer; (*c*) genetic linkage studies, gene identification, and tests for mutation status; (*d*) benefits of genetic testing, including the potential for early detection and reduction of uncertainty; (*e*) limitations of genetic testing, including incomplete penetrance (not all mutation carriers get cancer) and etiologic heterogeneity (noncarriers can still get cancer); (*f*) risks of genetic testing, including the potential for loss of insurance or employment and adverse psychosocial consequences for oneself and one's family; (*g*) options for prevention and surveillance and their limitations (including the possibility of peritoneal cystadenocarcinomatosis of the ovary); and (*h*) assurance of confidentiality of test results and related information.

After the education session, participants were given the option of receiving their *BRCA1* test results. To increase access to the counseling, test results were made available on the same day as the education session. This was possible because linkage results and mutational status had been determined as part of prior genetic studies and subsequently confirmed in an independent laboratory. Individuals had been informed in the introductory letter that results would be available. However, they were also informed that they could elect to receive their results at any time after receipt of pretest education. Because testing was conducted in the context of a research protocol, all testing and counseling were free of charge. In accordance with current guidelines,[25] all individuals who wished to receive their test results provided additional written informed consent.

Individuals who elected to receive their *BRCA1* test results participated in an individual counseling session with a physician/geneticist (H.T.L., S.N., or S.J.L.). The following topics were addressed according to a standardized counseling protocol: (*a*) patient expectations about the test result, (*b*) the test result and associated cancer risks for the individual and his or her offspring, (*c*) available options for surveillance and prevention and the associated limitations and risks, (*d*) the patient's plans for communicating his or her test results to others, (*e*) assertion of confidentiality of all test results and related information, and (*f*) supportive counseling as needed. All study subjects were recontacted for a telephone interview assessment of depression, functional health status, and medical decision making 1 month later.

Predictors of Utilization

All predictor variables were assessed at baseline, prior to the education session and the offer of receipt of *BRCA1* test results.

Sociodemographic and Clinical Variables.—Sex, age, education level, marital status, employment status, health insurance status, clinical status (affected vs unaffected), and number of first-degree relatives affected with breast or ovarian cancer were assessed.

Knowledge About Inherited Breast Cancer and *BRCA1* Testing.—An 11-item true-false measure was used to assess knowledge of inheritance of breast-ovarian cancer susceptibility and genetic testing. This measure has high internal consistency (coefficient α=.74). It includes items used in a core instrument developed for use by the National Center for Human Genome Research (NCHGR) Cancer Studies Consortium.

Perceptions of the Importance of the Benefits, Limitations, and Risks of *BRCA1* Testing.—A 12-item measure, developed and validated in previous research,[8,9] was used to assess attitudes about *BRCA1* testing. Subjects were offered a series of items enumerating potential benefits, limitations, and risks of *BRCA1* testing and were asked to indicate whether each was "not at all important," "somewhat important," or "very important" in their decision to have a *BRCA1* test. Principal components factor analysis indicated that this measure consists of 2 independent factors with a nonsignificant negative correlation. These 2 factors, labeled "perceptions of benefits" (pros) and "perceptions of limitations/risks" (cons) are highly internally consistent (coefficient α=.83 and .81, respectively).

Outcome Variables

***BRCA1* Testing Decisions.**—All subjects (including interview respondents and nonrespondents) were classified as either requesters or decliners of *BRCA1* testing. Requesters were those who received their *BRCA1* test results within the time frame of this study. Decliners were those who indicated that they did not wish to know their *BRCA1* mutation status at the present time. Status (request vs decline) was confirmed during the 1-month follow-up phone contacts.

Depression Symptoms.—The Center for Epidemiologic Studies Depression (CES-D) Scale was administered during the baseline and 1-month follow-up telephone interviews to assess depressive symptomatology. This scale has adequate test-retest reliability (r=0.57 for 2-8 weeks) and has been shown to correlate with clinical ratings of the severity of depression.[30] The Cronbach coefficient α in our sample was .91. Possible scores on this measure range from 0 to 60, with higher scores reflecting more depressive symptoms.

Functional Health Status.—Functional health status was assessed during the baseline and 1-month follow-up telephone interviews using 2 targeted scales from the Medical Outcomes Study (MOS).[31,32] The 4-item role functioning scale of the MOS was used as a measure of impairment in daily activities[31] (Cronbach coefficient α=.75). Scores on this measure range from 0 to 4. The 4-item sexual functioning scale was used because of the potential implications of *BRCA1* testing for reproductive and sexual functioning[32] (Cronbach coefficient α=.84). Scores on this measure range from 4 to 16. Both of these measures were scored such that higher scores reflected greater impairment in functioning.

Medical Decision Making.—During the 1-month follow-up interview, 2 individual items were administered to assess the impact of receipt of *BRCA1* test results on decisions about prophylactic mastectomy and prophylactic oophorectomy.

Statistical Analysis

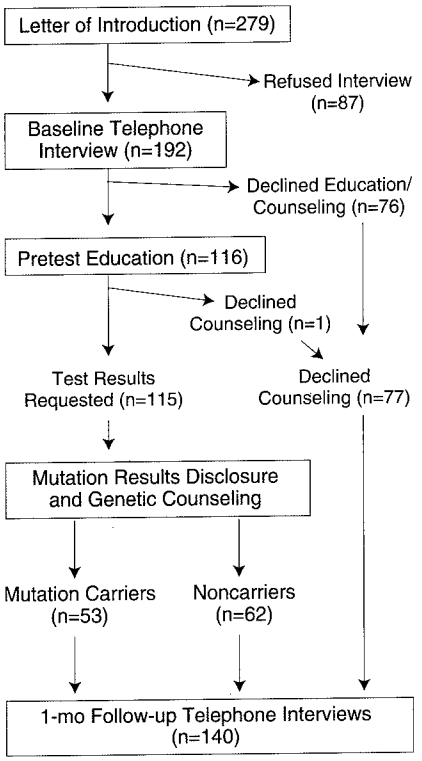
Descriptive statistics were used to determine the rates of participation and to characterize the study population in terms of knowledge of *BRCA1* testing and perceptions of the importance of the benefits, limitations, and risks of testing. Variables associated with *BRCA1* testing decisions were analyzed using χ^2 tests and t tests and by multivariate logistic regression models. Since members within a given family may have had correlated outcomes,[33,34] we used logistic regression analysis with general estimating equations[35] to account for intrafamily clustering.

The second stage of analysis focused on evaluating the psychosocial effects of *BRCA1* testing at 1-month follow-up. To identify possible baseline confounder variables, associations between study group (carrier, noncarrier, or decliner) and sociodemographic variables were assessed using χ^2 tests. Variables having significant associations with the study group were examined for their effects on 3 outcome variables (depressive symptoms, role impairment, and sexual impairment) using t tests and 1-way analyses of variance (ANOVAs). Next, 1-way ANOVAs were performed to test for differences between carriers, noncarriers, and decliners in terms of baseline psychological and functional status, as well as changes from baseline to 1-month follow-up. Linear regression analysis with general estimating equations[35] was used to examine changes in functioning while controlling for baseline levels, other potential confounder variables, and correlated responses within families. These analyses of the effects of testing were conducted for all study participants and then repeated excluding affected participants. Finally, effects of *BRCA1* testing on medical decision making in carriers and noncarriers were examined using an extension of the Fisher exact test.[36]

RESULTS

Response Rate to Baseline and Follow-up Interviews

As shown in Figure 1, of the 279 eligible men and women, 192 (69%) completed the baseline telephone interview, and 87 (31%) refused. Compared to interview respondents, nonrespondents were more likely to be male (χ^2=15.1;



Design of prospective study of *BRCA1* testing.

$P<.001$) and to have had a prior diagnosis of cancer ($\chi^2=4.4$; $P=.03$), but did not differ significantly in age. The vast majority of interview nonrespondents (81/87) also declined *BRCA1* test results when offered. Among the 192 individuals who completed the baseline interview, 140 (73%) were recontacted and completed the 1-month follow-up interview; the remaining subjects could not be reached after multiple attempts. Individuals lost to follow-up (n=52) were significantly more likely to have declined *BRCA1* testing (n=33) ($\chi^2=16.2$; $P<.001$), to be male (n=26) ($\chi^2=9.6$; $P=.002$), to lack health insurance (n=9) ($\chi^2=10.6$; $P=.001$), and to be unaffected (n=47) ($\chi^2=4.6$; $P=.03$). Individuals lost to follow-up were similar to remaining subjects with respect to any other demographic or clinical variables or in terms of the primary outcomes of depression and functional health status.

Sociodemographic Factors, Knowledge of *BRCA1* Testing, and Perceptions of the Importance of the Benefits and Limitations or Risks of Testing

The average (SD) age of interview respondents was 43 (14) years. All respondents were white, 67% were female, and 77% were married. Most (90%) had completed high school and most (93%) had health insurance.

Responses to the baseline knowledge measure are shown in Table 1. Scores on this measure ranged from 0 to 11, with an average (SD) score of 5.97 (2.91). Thus, on average, subjects gave correct responses to about 55% of the items. The percentage of subjects responding correctly to individual knowledge items ranged from 10% to 75%.

Table 1.—Descriptive Statistics for Baseline Knowledge Measure (n=192)

Item	Responding Correctly, No. (%)
True items	
A father can pass down an altered *BRCA1* gene to his daughters.	144 (75)
A woman who doesn't have an altered *BRCA1* gene can still get cancer.	142 (74)
A woman with an altered *BRCA1* gene has a high risk of ovarian cancer.	138 (72)
A woman who has a sister with an altered *BRCA1* gene has a 50% chance of having an altered gene herself.	113 (59)
Tests for ovarian cancer often do not detect a tumor until it has spread.	86 (45)
There are many different genes that cause cancer.	59 (31)
False items	
All women who have an altered *BRCA1* gene will get cancer.	115 (60)
A woman who gets breast cancer at age 70 years is more likely to have an altered *BRCA1* gene than a woman who gets breast cancer at age 40 years.	113 (59)
Having one's ovaries removed will definitely prevent cancer.	59 (31)
The *BRCA1* gene causes about one half of all breast cancers.	33 (17)
About 1 in 10 women have an altered *BRCA1* gene.	19 (10)

As shown in Table 2, the benefit of *BRCA1* testing rated as most important was "to learn about my children's risks" (rated by 96% of participants as somewhat or very important). The most important perceived limitation or risk of testing was "test results might not be accurate" (rated by 40% of participants as somewhat or very important). The possibility of losing health insurance was rated as a somewhat or very important limitation or risk of testing by 34% of the sample. Interestingly, individuals with and without health insurance endorsed this item at the same rate. Scores for the perception of benefits scale and the perception of limitations or risks scale ranged from 6 to 18, with average (SD) scores of 15.30 (2.78) and 8.47 (2.48), respectively. Overall, individuals rated the benefits of testing as significantly more important than the limitations or risks of testing ($t_{190}=2.71$; $P=.007$).

Utilization of *BRCA1* Testing

The rates of participation and *BRCA1* testing decisions are shown in Figure 1. Among all family members offered the opportunity to receive their *BRCA1* test results (n=279), 43% requested their test results (n=121), and 57% declined (n=158). The rate of requests for testing was higher when the denominator included only those individuals who participated in the baseline interview (n=192). In this sample of respondents, 116 individuals (60%) opted to receive pretest education and all but 1 of these decided to obtain the results of testing. The results presented below compare baseline interview respondents who elected to receive *BRCA1* test results (n=115; 60%) with those who declined (n=77; 40%). Of those who received the test results, 46% (n=53) were mutation carriers and 54% (n=62) were noncarriers. Information on specific mutations has been previously reported.[27]

Predictors of Utilization of *BRCA1* Testing

The results of the bivariate analyses of *BRCA1* testing decisions are shown in Table 3. *BRCA1* test use was associated with female sex, having a high school education or beyond, and having health insurance. Having a greater number of first-degree relatives with breast cancer was positively related to test use, while the number of relatives with ovarian cancer was not. There was a marginal association ($P=.053$) between test use and clinical status (affected vs unaffected). Marital status and employment were unrelated to *BRCA1* testing. Baseline knowledge about *BRCA1* testing ($t_{190}=4.46$; $P<.001$) and perceived importance of the benefits of testing ($t_{190}=2.76$; $P=.006$) both related strongly to test use, while the perceived importance of the limitations or risks of testing was not.

To identify factors having independent associations with *BRCA1* testing decisions, predictor variables with $P<.10$ associations in bivariate analyses were tested in logistic regression models (Table 4). Significant independent predictors of test use in this model included the number of first-degree relatives with breast cancer (OR, 1.59; 95% confidence interval [CI], 1.16-2.16) and having health insurance (OR, 3.74; 95% CI, 2.06-6.80). Knowledge of *BRCA1* testing and perceived importance of the benefits of testing both exhibited independent positive associations with *BRCA1* test use (OR, 1.85; 95% CI, 1.36-2.50 and OR, 1.45; 95% CI, 1.13-1.86, respectively). Odds ratios for these continuous measures were based on a 1 SD difference in scale scores. Thus, individuals who scored 1 SD above the mean on either knowledge of *BRCA1* testing or the perceived benefits of testing were 1.5 to 2 times more likely to use *BRCA1* testing than individuals scoring at the mean.

Table 2.—Descriptive Statistics for Perceived Importance of the Benefits, Limitations, and Risks of *BRCA1* Testing (n=192)

Variable	No. (%) Endorsing Level of Importance		
	Not at All	Somewhat	Very
Benefits of testing			
To learn about my children's risk	8 (4)	35 (18)	149 (78)
To know if I need to increase screening	14 (7)	44 (23)	134 (70)
To plan for the future	17 (9)	46 (24)	129 (67)
To make surgery decisions*	14 (15)	21 (22)	59 (63)
To be reassured	17 (9)	58 (30)	117 (61)
To make childbearing decisions†	41 (39)	21 (20)	44 (41)
Limitations and risks of testing			
Worried about losing insurance	126 (66)	35 (18)	31 (16)
Concerns about effect on family	121 (63)	42 (22)	29 (15)
Don't believe I can prevent getting cancer	130 (68)	44 (23)	18 (9)
Couldn't handle it emotionally	132 (69)	44 (23)	16 (7)
Test results might not be accurate	115 (60)	63 (33)	14 (7)
Don't trust modern medicine	161 (84)	23 (12)	8 (4)

*Women only.
†Men and women who had not completed their families.

Table 3.—Predictors of Utilization of *BRCA1* Testing

Variable	Subgroup	Request, No. (%) (n=115)	Decline, No. (%) (n=77)	χ^2	Odds Ratio (95% CI)*	*P* Value
Sex	Female	85 (66)	44 (34)	5.88	2.10 (1.15-3.92)	.01
	Male	30 (48)	33 (52)			
Age, y	<50	91 (63)	53 (37)	2.61	1.72 (0.88-3.32)	.11
	≥50	24 (50)	24 (50)			
Education	≥High school	110 (62)	67 (38)	6.08	4.10 (1.24-13.7)	.01
	<High school	4 (29)	10 (71)			
Marital status	Married	92 (63)	55 (37)	2.23	1.67 (0.85-3.30)	.13
	Unmarried	22 (50)	22 (50)			
Employment	Not employed	32 (65)	17 (35)	0.80	1.36 (0.70-2.67)	.37
	Employed	83 (58)	60 (42)			
Health insurance	Yes	111 (62)	67 (38)	6.17	4.14 (1.25-13.70)	.01
	No	4 (29)	10 (71)			
Clinical status	Affected	28 (74)	10 (26)	3.75	2.15 (0.99-4.74)	.05
	Unaffected	87 (56)	67 (44)			
No. of first-degree relatives with breast cancer	≥2	39 (75)	13 (25)	6.28	2.45 (1.21-4.98)	.01
	0-1	76 (55)	62 (45)			
No. of first-degree relatives with ovarian cancer	≥2	3 (60)	2 (40)	.005	0.94 (0.15-5.88)	.94
	0-1	112 (62)	70 (38)			

	Request, Score Mean (SD)	Decline, Score Mean (SD)	*t* Test†	*P* Value
Knowledge	6.71 (2.72)	4.88 (2.85)	4.46	<.001
Perceived benefits	15.74 (2.62)	14.63 (2.90)	2.76	.006
Perceived limitations and risks	8.34 (2.60)	8.66 (2.29)	−0.88	.38

*CI indicates confidence interval.
†Degrees of freedom are 190.

Table 4.—Logistic Regression Analysis of *BRCA1* Test Use

Variable	Estimate	SE	Odds Ratio (95% CI)*
Constant	−4.58	1.99	. . .
Sex, F/M	0.44	0.41	1.55 (0.69-3.49)
Health insurance, yes/no	1.32	0.30	3.74 (2.06-6.80)
Education, ≥/<high school	1.26	0.73	3.52 (0.84-14.69)
Clinical status, affected/unaffected	0.003	0.40	1.01 (0.46-2.18)
No. of first-degree relatives with breast cancer†	0.46	0.16	1.59 (1.16-2.16)
Knowledge‡	0.21	0.05	1.85 (1.36-2.50)
Perceived benefits of testing‡	0.13	0.05	1.45 (1.13-1.86)

*CI indicates confidence interval.
†Odds ratios reflect the increase in odds associated with each additional first-degree relative.
‡Odds ratios reflect the increase in odds associated with 1 SD increase in the continuous measure.

Education level and sex did not enter this adjusted model, despite significant bivariate associations with *BRCA1* test use. This may be due to multicollinearity with the knowledge variable. The model was repeated excluding affected subjects and the results were similar.

Psychosocial Outcomes of *BRCA1* Testing

To identify potential baseline confounder variables, we compared the 3 study groups (carriers, noncarriers, and decliners) with respect to sociodemographic and clinical variables. Only 2 variables had significant associations with the 3-level study group variable: clinical status (affected vs unaffected) (χ^2=31.8; P<.001) and number of affected first-degree relatives (χ^2=10.7; P=.03). Not surprisingly, carriers had a significantly greater number of affected first-degree relatives than noncarriers or decliners and were more likely to be affected themselves. However, neither of these 2 variables was associated with changes in depression, role impairment, or sexual impairment and therefore would not be likely confounder variables. Nonetheless, because of the increased relevance of *BRCA1* testing for unaffected individuals, we conducted 2 sets of outcome analyses: 1 set of analyses for all subjects and 1 set for unaffected individuals only. The latter set of analyses also served to control for heterogeneity that potentially could mask meaningful between-group differences in psychosocial outcomes.

The psychological and functional health status outcomes by study group (carrier, noncarrier, and decliner) are shown in Table 5. The study groups had similar baseline levels of depression and sexual impairment, but differed at baseline with respect to role impairment; ie, noncarriers had higher baseline levels of role impairment ($F_{2,137}$=3.59; P=.03). Baseline levels for all measures were within the normal ranges.[30-32] In the analysis of all subjects, significant between-group differences in changes from baseline to 1-month posttesting were observed for role impairment ($F_{2,137}$=8.61; P<.001). Nonsignificant between-group differences in change scores were observed for depression ($F_{2,137}$=2.83; P=.06) and sexual impairment ($F_{2,116}$=2.39; P=.10). Among unaffected subjects, significant between-group differences in change scores were observed for depression ($F_{2,104}$=3.00; P=.05) and role impairment ($F_{2,104}$=7.39; P=.001). A nonsignificant between-group difference in change scores was observed for sexual impairment ($F_{2,83}$=2.68; P=.07). As shown in Table 5, noncarriers and carriers in unaffected subjects both showed consistent reductions in all 3 measures of

Table 5.—Psychological and Functional Health Status by Study Group

Variable*	All Study Participants							Unaffected Study Participants						
	Noncarriers, Score Mean (SD)	No.	Carriers, Score Mean (SD)	No.	Decliners, Score Mean (SD)	No.	P Value	Noncarriers, Score Mean (SD)	No.	Carriers, Score Mean (SD)	No.	Decliners, Score Mean (SD)	No.	P Value
Depression (range, 0-60)														
Baseline	8.70 (9.47)	50	8.19 (8.37)	46	7.15 (10.15)	44	.72	8.68 (9.56)	47	7.04 (6.34)	22	7.49 (10.50)	38	.75
1 mo†	−3.39 (10.07)	50	−0.10 (7.45)	46	0.37 (7.23)	44	.06	−3.58 (10.07)	47	−0.19 (6.42)	22	0.77 (7.31)	38	.05
Role impairment (range, 0-4)														
Baseline	1.32 (1.19)	50	0.97 (1.02)	46	0.70 (1.13)	44	.03	1.30 (1.18)	47	1.00 (1.02)	22	0.71 (1.18)	38	.07
1 mo†	−0.94 (1.18)	50	−0.13 (1.27)	46	0.00 (1.14)	44	<.001	−0.96 (1.21)	47	−0.13 (1.28)	22	0.00 (1.18)	38	.001
Sexual impairment‡ (range, 4-16)														
Baseline	5.56 (3.05)	47	6.02 (2.85)	37	5.04 (1.75)	35	.30	5.16 (3.11)	45	5.50 (2.14)	18	4.99 (1.76)	31	.57
1 mo†	−0.80 (3.33)	47	−0.66 (2.53)	37	0.76 (3.91)	35	.09	−0.82 (3.37)	45	−0.82 (2.32)	18	1.01 (4.08)	31	.07

*The variable for depression is based on the Center for Epidemiologic Studies Depression Scale. The variables for role impairment and sexual impairment are based on scales from the Medical Outcomes Study.
†Scores shown are changes from baseline to 1-month follow-up. Higher scores reflect more impairment.
‡These items had "not applicable" responses from 21 of the subjects.

distress and impairment (reflected in negative change scores), while decliners showed small increases or no change.

Multiple linear regression models were generated to predict changes in each of the 3 psychosocial outcome variables (depression, role impairment, and sexual impairment); these models examined the effect of study group while controlling for baseline levels of the outcome variable. In the analyses of all subjects, noncarriers exhibited significantly greater reduction in depression than both carriers and decliners (β=3.07, P<.001; β=3.10, P<.001, respectively). Noncarriers also exhibited significantly greater reduction in role impairment than both carriers and decliners (β=.55, P=.001; β=.60, P=.004, respectively). For sexual impairment, noncarriers exhibited significantly greater reductions than decliners (β=1.17; P=.03), but did not differ from carriers. Those identified as carriers did not show increases in depression and functional impairment. When conducted with unaffected individuals only, results for depression did not change. Role impairment differed only between noncarriers and carriers, and there were no significant differences between the 3 groups of unaffected individuals in sexual impairment.

Medical Decision Making

The impact of *BRCA1* testing on prophylactic surgery decisions was examined for unaffected women who received their *BRCA1* test results. As shown in Table 6, 17% of carriers reported that they intended to obtain prophylactic mastectomies and 33% intended to obtain prophylactic oophorectomies. An additional 17% of carriers remained undecided. None of the noncarriers intended to have prophylactic surgery. It is notable that of 9 unaffected women who had previously opted for prophylactic mastectomies, 5 were determined to be carriers and 4 were noncarriers of a *BRCA1* mutation. Of the 15 women who had previous oophorectomies, 4 were determined to be carriers and 11 were noncarriers.

COMMENT

Forty-three percent of all individuals from HBOC families requested *BRCA1* test results when offered. Among individuals who agreed to participate in a baseline telephone interview, 60% requested test results. While these rates are somewhat lower than predicted based on prior surveys of interest in *BRCA1* testing in HBOC families,[10] they exceed the rates of uptake for other new genetic tests such as those for the *HD* and *CF* genes.[11-14] This is not surprising considering key differences between breast cancer and other genetic disorders. For example, unlike Huntington disease and cystic fibrosis, there are options available for potentially reducing breast cancer risk; if breast cancer is found early, treatment may be effective.

There are other possible explanations for the higher rates of *BRCA1* test use in this study. First, subjects were members of a hereditary cancer registry and had provided blood samples for previous genetic studies.[27-29] They were also aware that *BRCA1* test results would be available on the same day as the pretest education. Utilization of carrier testing has been shown to increase when the offer of test results is immediate vs delayed.[13,14] Second, testing was offered in the context of a research study and was therefore free of cost. The cost of commercial *BRCA1* testing may range from approximately $150 to $1500, depending on whether the specific mutation in the family has been identified.[37] This cost may be a deterrent for some individuals. While some insurance companies may pay for testing and counseling services, patients may be reluctant to request such payment because of concerns about future genetic discrimination.

The results of this study provide some insights into the characteristics of individuals likely to come forward for *BRCA1* testing. In the bivariate analyses, women were about twice as likely to request test results as men. The lower rate of test use among men may be because they perceive themselves as less vulnerable to the effects of *BRCA1* mutations.[10] Had we included information in the initial letter to family members about prostate and colon cancer and paternal transmission of susceptibility, the rate of participation of men in the education session and subsequent testing might have increased (these issues were discussed in the education sessions). Individuals who had been affected with cancer requested test results at a higher rate than unaffected at-risk individuals. Requests for *BRCA1* test results were significantly more frequent among individuals with a greater number of relatives affected with breast cancer.

The potential for discrimination by health insurers on the basis of genetic status is considered to be one of the most serious risks of *BRCA1* testing.[18,38] Consistent with this, our results suggest that the lack of health insurance may be a significant barrier to participation in *BRCA1* testing programs. Individuals who did not have health insurance were almost 4 times less likely to request *BRCA1* testing than individuals with health insurance, even after adjusting for other sociodemographic factors. Moreover, 34% of individuals reported at baseline that the possibility of losing health insurance was an important risk in having *BRCA1* testing. Concerns about insurance discrimination may also deter carriers of *BRCA1*

Table 6.—Impact of *BRCA1* Testing on Prophylactic Surgery Decisions Among Unaffected Women

Variable	Carriers, No. (%)	Noncarriers, No. (%)	*P* Value*
Decided to obtain prophylactic mastectomy			
Yes	2 (17)	0 (0)	
No	8 (66)	30 (100)	.003
Uncertain	2 (17)	0 (0)	
Decided to obtain prophylactic oophorectomy			
Yes	4 (33)	0 (0)	
No	6 (50)	22 (100)	.001
Uncertain	2 (17)	0 (0)	

*This value was obtained using the Fisher exact test for 2×3 contingency table.

mutations from sharing their mutation status with their providers and insurers and from undergoing potentially beneficial preventive interventions.[39] Also, individuals who know their mutation status and deliberately withhold such information from insurance companies could risk the loss of their policy or coverage for an illness related to the mutation. Individuals who lacked health insurance may also have been deterred by the cost of subsequent medical care that might be indicated if they tested positive.

The results of this study also shed light on how patients process information in making their decisions about *BRCA1* testing. Individuals with more knowledge about HBOC and genetic testing and those who rated the benefits of *BRCA1* testing as significantly more important than the limitations and risks were more likely to request *BRCA1* test results. Thus, to the extent that the public is educated about *BRCA1* testing and the potential benefits are emphasized, utilization of *BRCA1* testing is likely to increase. Contrary to our expectations and previous research,[21,22] we found that the perceived importance of the limitations and risks of *BRCA1* testing did not influence *BRCA1* testing decisions. In addition, subjects rated the limitations and risks of *BRCA1* testing as statistically significantly less important than the benefits. This is despite the fact that the limitations and risks of *BRCA1* testing were emphasized in all contacts, including those prior to our assessments. Thus, it appears that *BRCA1* testing decisions were influenced disproportionately by the benefits of testing, relative to the limitations and risks of testing.

Another goal of this study was to evaluate the effects of *BRCA1* testing on psychological and functional health status and on patients' medical decisions. The results of these analyses do not provide evidence for serious short-term adverse effects of *BRCA1* testing, at least among high-risk individuals. Carriers of *BRCA1* mutations showed no increases in depressive symptoms and functional impairment by 1 month following disclosure of test results. Improvements in psychosocial functioning were statistically significant for noncarriers. Individuals who declined *BRCA1* test results experienced no changes in depression or functional health status. As was found for genetic testing for Huntington disease (the *HD* gene),[23] learning one's *BRCA1* genetic status may reduce prolonged uncertainty and thereby enhance quality of life. This may be true even when the result reveals a risk-conferring mutation.

The results of *BRCA1* testing may also be useful to carriers in decision making about prophylactic surgery. In the present study, 33% of carriers reported that they planned to obtain prophylactic oophorectomies and 18% intended to obtain prophylactic mastectomies. For members of HBOC families who do not carry a *BRCA1* mutation, receipt of a negative test result may prevent unnecessary prophylactic surgery.[19]

While these outcomes are encouraging, they must be considered in the proper context. First, participants in this study were members of high-risk families in a hereditary cancer registry, many of whom were involved in prior cancer genetics studies. All of these individuals were white and most had a high school education. These factors may limit the generalizability of the study findings. Second, in accordance with current guidelines,[25,26] all testing was provided as part of a carefully monitored research protocol including pretest education and genetic counseling. Such counseling may be responsible for the psychosocial benefits observed at 1-month follow-up. Outside a controlled research environment or in the general population, the potential for adverse effects of *BRCA1* testing may be greater. Third, outcome data for this study were collected 1 month after *BRCA1* testing and different results may be found with longer-term follow-up. However, based on studies of Huntington disease genetic testing,[23] the psychological benefits would be expected to increase, rather than decrease, over time. Finally, the results of the present study may have been influenced by a response bias. A subset of eligible individuals (31%) elected not to participate in the baseline interview; the vast majority of these individuals also declined *BRCA1* testing. The model of *BRCA1* test decision making might have differed had these individuals been included in the analysis. On the other hand, individuals who withdrew from the study (most of whom declined test results) did not differ in terms of their demographic backgrounds or in psychological or functional profiles from those who remained. Therefore, significant bias in the results of the psychosocial outcomes analysis is unlikely.

Although the results of the outcome analysis provide information about overall responses to *BRCA1* testing, additional studies are needed to examine individual differences among testing participants. The SDs in depressive symptoms and other outcomes suggested the presence of a moderate degree of within-group variability. Thus, it is likely that persons with different educational backgrounds or with different psychological profiles responded differently to learning their *BRCA1* mutation status.[20] Information about such differences would be very useful to identify individuals who are more or less vulnerable to adverse effects of *BRCA1* testing and to tailor counseling and follow-up accordingly. Future studies should also examine more subtle effects of *BRCA1* testing on carriers and noncarriers, including guilt, anger, and strained family relationships.[19]

CONCLUSIONS

Our findings suggest that some, but not all, members of HBOC families will want to have *BRCA1* testing. Rates of *BRCA1* test use may be highest for individuals of a higher socioeconomic status and those who have a greater number of relatives affected with breast cancer. Individuals who lack health insurance may be deterred from *BRCA1* testing because of concerns about genetic discrimination in employment and insurance. This inequity in access to testing will be best addressed by federal legislation prohibiting insurance companies from using genetic information to establish eligibility for enrollment or continuation of insurance or to determine premium rates.[40]

Although the findings related to the psychosocial impact of *BRCA1* testing in HBOC families are promising, the complexities of testing and counseling must be considered carefully prior to extending these services outside the context of carefully monitored research protocols.[41] The high frequency of *BRCA1* mutations found in women of Ashkenazi Jewish descent,[42,43] coupled with the recent availability of commercial testing and the widespread publicity about *BRCA1* testing,[37] may create strong pressures for physicians to offer testing. However, prior to the translation of *BRCA1* technology from research to clinical practice, strategies for patient education and informed consent must be developed and tested. The results of

the present study underscore the importance of conveying information, not only about the benefits of testing, but particularly about the limitations and risks of these tests. Individuals who elect to receive their test results should be counseled extensively about the implications of these results, as well as about the limitations and risks of available surgical and prevention options.[17] Proper informed consent and counseling is essential to optimize patient decisions about *BRCA1* testing, thereby maximizing the potential benefits and minimizing the risks of this new technology.

This work was supported by Department of Defense grants DAMD17-94-J-4340 and DAD17-94-J-4299; Nebraska State Cigarette Tax Cancer and Smoking-Related Disease Program grant LB595 and Council for Tobacco Research funding; National Cancer Institute grant CA01604; and National Institute of Mental Health grant MH54435.

We wish to thank Aba Bonney for assistance with telephone interviewing and Susan Marx and Theresa Brownson for their assistance with manuscript preparation. We also thank Patrice Watson, PhD, for her efforts with study development. We also appreciate the feedback provided by Gary Chase, PhD, Marc Schwartz, PhD, and Madison Powers, PhD, on an earlier version of the manuscript. We wish to acknowledge the valuable input of the Cancer Genetic Studies Consortium and the Ethical, Legal, and Social Implications (ELSI) program of the National Center for Human Genome Research. We also are very grateful to all of the family members who participated in this study.

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Printed and Published in the United States of America